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# CANADIAN PATENT

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SKIN BLEACHING COMPOSITION

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Canada

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SKIN BLEACHING COMPOSITION

Abstract of the Disclosure

A synergistic skin-bleaching composition for use by topical application has been found which comprises a mixture of a bleaching agent, a skin irritant-exfoliating agent and an anti-inflammatory agent formulated in a pharmaceutically-cosmetically acceptable vehicle. The composition comprising 2% hydroquinone, 0.05% retinoic acid and either 0.025% dexamethasone or fluorometholone was particularly effective.

Background of the Invention

1) Field of the Invention: This invention relates to a new synergistic skin-bleaching composition for use by topical application.

2) Description of the Prior Art: So-called compositions for the bleaching of skin have been known for many years, if not centuries. The prior art contains many references to the use of hydroquinone and its derivatives as agents in bleaching creams, etc., the most pertinent of which are:

a) U. S. Patent No. 3,060,097, issued October 23, 1962 to a skin-bleaching composition comprising sodium hypochlorite, hydroquinone monobenzyl ether and a "penetrant". Three British Patents No.'s 763,029, 855,431 and 965,869 issued to the same inventor on similar compositions.

b) French Patent No. 1,513,395, issued January 8, 1968 to a skin-bleaching composition comprising hydroquinone monobenzyl ether or a derivative thereof in combination with tyrothricin or a derivative thereof.

c) French Patent No. 1,270,854, issued July 24, 1961 to

1 a skin-bleaching composition comprising hydroquinone benzyl  
2 ether (l'ether de benzylhydroquinone) and an anti-oxidant.  
3 The product may be formulated to contain vitamins, amino  
4 acids, cholesterol, etc.

5 d) United States Patents No. 2,274,725 (March 31, 1942),  
6 2,376,884 (May 29, 1945) and 2,377,188 (May 29, 1945) are to sun-  
7 screen preparations comprising hydroquinone as the active sun-  
8 filter agent. These preparations are stabilized by the addition  
9 of certain anti-oxidants.

10 e) Zschr. Haut-Geschl.-Krh. 42, 17: 711-716 reports  
11 studies of bleaching the skin using hydroquinone monobenzyl  
12 ether. When a subject was found to have sensitive skin, 5%  
13 hydroquinone monobenzyl ether and 4% prednisolone was used to  
14 prevent or control the contact dermatitis produced by the hydro-  
15 quinone monobenzyl ether. No mention is made of an improved  
16 bleaching effect when the preparation contained prednisolone.

17 f) Some other articles reporting on skin-bleaching by the  
18 use of hydroquinone or its derivatives are:

- 19 1. Archives of Dermatology, 84, No. 1, 131-134 (July  
20 1961).
- 21 2. Clinical Medicine, 70, No. 6, 1111-1114 (June 1963).
- 22 3. Clinical Medicine, 72, No. 3, 87-88 (March 1966).
- 23 4. Postgraduate Medicine, 37, No. 2, 198-201 (February  
24 1965).
- 25 5. J. Investigative Medicine, 18, 119-135 (1952).
- 26 6. J. Am. Medical Assoc., 152, No. 7, 577-582 (June  
27 13, 1953).
- 28 7. Dermatologica, 134, 125-128 (1967).
- 29 8. Archives of Dermatology, 93, No. 5, 589-600 (May  
30 1966).

1 The above cited art constitutes but a small portion of the  
2 prior art but is representative of that deemed most pertinent.  
3 None of the above teaches or anticipates the three component  
4 synergistic compositions of the present invention.

5 Summary of the Invention  
6

7 A synergistic skin-bleaching composition for external appli-  
8 cation has been found comprising a bleaching agent selected from  
9 the group comprising hydroquinone, hydroquinone monomethyl ether,  
10 hydroquinone monoethyl ether and hydroquinone monobenzyl ether,  
11 a skin irritant-exfoliating agent and an anti-inflammatory cor-  
12 ticosteroid.

13 Complete Disclosure

14 It has long been desirable in certain skin disorders or  
15 diseases to be able to depigment (bleach) the skin to remove  
16 certain disfiguring blemishes generally caused by the deposi-  
17 tion of excess quantities of melanin. This hyperpigmentation  
18 is generally viewed as cosmetically undesirable or psychologi-  
19 cally disabling. Examples of these blemishes would be freckles,  
20 senile lentigo, lentigines (liver spots), melasma, contact  
21 allergy pigmentation, sunburn pigmentation, post-inflammatory  
22 hyperpigmentation due to abrasion, burns, wounds, dermatitis,  
23 phototoxic reaction and other similar small, fixed pigmented  
24 lesions. Likewise, it is also desirable to be able to decolorise  
25 normally pigmented skin to generally increase "fairness" of  
26 appearance and to blend hypopigmented areas into surrounding  
27 bleached skin. This is particularly so in the treatment of  
28 negroes, brown-skin people, or generally dark skinned people  
29 suffering from vitiligo.

30 It was an object of the present invention to prepare an



1 effective and superior product as compared to those currently  
2 on the market or known in the literature.

3 ~~The compounds hydroquinone, hydroquinone monomethyl ether,~~  
4 ~~hydroquinone monobenzyl ether, ammoniated mercury, zinc peroxide,~~  
5 ~~red mercuric oxide, sodium hypochlorite, hydrogen peroxide, mer-~~  
6 ~~curous chloride and bichloride of mercury are all known in the~~  
7 ~~literature as bleaching agents of the skin. Only hydroquinone~~  
8 ~~is recognized as a bleaching agent possessing satisfactory~~  
9 ~~qualities.~~

10 The object of the present invention has been achieved by the  
11 formulation of a superior synergistic skin-bleaching composition  
12 for external application which comprises a mixture of a bleaching  
13 agent, a skin irritant-exfoliating agent and an anti-inflammatory  
14 agent in a pharmaceutically-cosmetically acceptable vehicle.

15 A preferred embodiment of the present invention is a syner-  
16 gistic skin-bleaching composition for external application com-  
17 prising a bleaching agent selected from the group comprising  
18 hydroquinone, hydroquinone monomethyl ether, hydroquinone mono-  
19 ethyl ether and hydroquinone monobenzyl ether, a skin irritant-  
20 exfoliating agent and an anti-inflammatory corticosteroid for-  
21 mulated in a pharmaceutically-cosmetically acceptable vehicle.

22 Another preferred embodiment is a synergistic skin-bleaching  
23 composition for external application comprising about 1% to about  
24 10% of a bleaching agent selected from the group comprising hydro-  
25 quinone, hydroquinone monomethyl ether, hydroquinone monoethyl  
26 ether and hydroquinone monobenzyl ether, and about 0.025% to about  
27 80% of a skin irritant-exfoliating agent and about 0.01% to about  
28 3.0% of an anti-inflammatory corticosteroid formulated in a phar-  
29 maceutically-cosmetically acceptable vehicle.

30 Another preferred embodiment is a synergistic skin-bleaching

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1 composition for external application comprising about 1% to  
2 about 5% of a bleaching agent selected from the group comprising  
3 hydroquinone, hydroquinone monomethyl ether, hydroquinone mono-  
4 ethyl ether and hydroquinone monobenzyl ether, about 0.025% to  
5 about 15% of a skin irritant-exfoliating agent selected from  
6 the group comprising unsaturated fatty acids, long chain fatty  
7 acid esters or salts thereof, retinoic acid, oleic acid, arachi-  
8 donic acid, polyoxyethylene lauryl or myristyl ethers, alkyl-  
9 amines containg 5 to 16 carbon atoms, salicylic acid and benzoic  
10 acid, and about 0.01% to about 3.0% of an anti-inflammatory  
11 corticosteroids selected from the group comprising hydrocorti-  
12 sone, cortisone, prednisolone, prednisone, dexamethasone, beta-  
13 methasone, fluocinolone acetonide, triamcinolone, fluocinolone,  
14 triamcinolone acetonide, methylprednisolone, fluorometholone,  
15 or an ester thereof when chemically possible, formulated in a  
16 pharmaceutically-cosmetically acceptable vehicle.

17 A more preferred embodiment is a synergistic skin-bleaching  
18 composition for external application comprising about 1% to about  
19 5% of hydroquinone, about 0.020% to about 10% of a skin irritant-  
20 exfoliating agent selected from the group comprising retinoic  
21 acid, arachidonic acid, oleic acid, linoleic acid, linolenic  
22 acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate,  
23 polyoxyethylene lauryl ether, polyoxyethylene myristyl ether,  
24 salicylic acid, benzoic acid, and n-octylamine, and about 0.01% to  
25 about 3% of an anti-inflammatory corticosteroid selected from the  
26 group comprising dexamethasone, betamethasone, fluocinolone, flu-  
27 cinolone acetonide, triamcinolone, hydrocortisone, triamcinolone,  
28 acetonide, fluorometholone, or an ester thereof when chemically possible,  
29 formulated in a pharmaceutically-cosmetically acceptable vehicle.

30 A most preferred embodiment is the synergistic skin-bleaching

1 composition for external application comprising about 2% hydro-  
2 quinone, about 0.05% retinoic acid and about 0.025% fluorometholone  
3 formulated in a pharmaceutically-cosmetically acceptable vehicle

4 Another most preferred embodiment is the synergistic skin-  
5 bleaching composition for external application comprising about  
6 2% hydroquinone, about 0.05% retinoic acid and about 0.025%  
7 dexamethasone formulated in a pharmaceutically-cosmetically  
8 acceptable vehicle.

9 Still another most preferred embodiment is the synergistic  
10 skin-bleaching composition for external application comprising  
11 about 2% hydroquinone, about 0.05% retinoic acid and about 2.5%  
12 hydrocortisone or hydrocortisone acetate formulated in a phar-  
13aceutically-cosmetically acceptable vehicle.

14 A preferred embodiment of the present invention is a method  
15 of bleaching human skin by applying to the skin a synergistic  
16 skin-bleaching composition which comprises a mixture of a bleaching  
17 agent, a skin irritant-exfoliating agent and an anti-inflammatory  
18 agent formulated in a pharmaceutically-cosmetically acceptable  
19 vehicle.

20 Another preferred embodiment is the method of bleaching  
21 human skin wherein the bleaching composition comprises a  
22 bleaching agent selected from the group comprising hydroquinone,  
23 hydroquinone monomethyl ether, hydroquinone monoethyl ether and  
24 hydroquinone monobenzyl ether, a skin irritant-exfoliating agent  
25 and an anti-inflammatory corticosteroid formulated in a phar-  
26aceutically-cosmetically acceptable vehicle.

27 A further preferred embodiment is the method of bleaching  
28 human skin wherein the bleaching composition comprises about 1%  
29 to about 10% of a bleaching agent selected from the group com-  
30prising hydroquinone, hydroquinone monomethyl ether, hydroquinone



1 monoethyl ether and hydroquinone monobenzyl ether, and about 0.025%  
 2 to about 80% of a skin irritant-exfoliating agent and 0.01% to about  
 3 3.0% of an anti-inflammatory corticosteroid formulated in a pharma-  
 4 ceutically-cosmetically acceptable vehicle.

5 A more preferred embodiment is the method of bleaching human  
 6 skin wherein the bleaching composition comprises about 1% to about  
 7 5% of a bleaching agent selected from the group comprising hydroquinone,  
 8 hydroquinone monoethyl ether, hydroquinone monoethyl ether and hydro-  
 9 quinone monobenzyl ether, about 0.025% to about 15% of a skin irri-  
 10 tant-exfoliating agent selected from the group comprising unsaturated  
 11 fatty acids, long chain fatty acid esters or salts thereof, retinoic  
 12 acid, arachidonic acid, polyoxyethylene lauryl or myristyl ethers,  
 13 oleic acid, alkylamines containing 5 to 16 carbon atoms, salicylic  
 14 acid and benzoic acid, and about 0.1% to about 3.0% of an anti-  
 15 inflammatory corticosteroids selected from the group comprising  
 16 hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone,  
 17 betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone,  
 18 triamcinolone acetate, methylprednisolone, fluorometholone, or an  
 19 ester thereof when chemically possible, formulated in a pharmaceu-  
 20 tically-cosmetically acceptable vehicle.

21 Another more preferred embodiment is the method of bleaching  
 22 human skin wherein the bleaching composition comprises about 1% to  
 23 about 5% of hydroquinone, about 0.020% to about 10% of a skin irri-  
 24 tant-exfoliating agent selected from the group comprising retinoic  
 25 acid, arachidonic acid, linoleic acid, oleic acid, linolenic acid,  
 26 sodium lauryl sulfate, dioctyl sodium sulfosuccinate, polyoxy-  
 27 ethylene lauryl ether, polyoxyethylene myristyl ether, salicylic  
 28 acid, benzoic acid, and n-octylamine, and about 0.01% to about  
 29 3% of an anti-inflammatory corticosteroid selected from the group  
 30 comprising dexamethasone, betamethasone, fluocinolone, fluocinolone

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1 acetone, triamcinolone, hydrocortisone, triamcinolone acetate,  
2 fluorometholone, or an ester thereof when chemically possible,  
3 formulated in a pharmaceutically-cosmetically acceptable vehicle.

4 A most preferred embodiment is the method of bleaching  
5 human skin wherein the bleaching composition comprises about  
6 2% hydroquinone, about 0.05% retinoic acid and about 2.5%  
7 hydrocortisone or hydrocortisone acetate formulated in a phar-  
8 maceutically-cosmetically acceptable vehicle.

9 A most preferred embodiment is the method of bleaching  
10 human skin wherein the bleaching composition comprises about  
11 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluoro-  
12 metholone formulated in a pharmaceutically-cosmetically acceptable  
13 vehicle.

14 Another most preferred embodiment is the method of bleaching  
15 human skin wherein the bleaching composition comprises about 2%  
16 hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone  
17 formulated in a pharmaceutically-cosmetically acceptable vehicle.

18 Hydroquinone, hydroquinone monomethyl ether and hydro-  
19 quinone monobenzyl ether are all known in the literature as  
20 bleaching agents for lightening of the skin. While there is  
21 some question as to the mode of action of these agents and treat-  
22 ment is considered an "art" rather than a science, it is generally  
23 thought that all of these agents work through the common inter-  
24 mediate hydroquinone. Additionally, it is known that hydro-  
25 quinone is the least irritating of these hydroquinones, the  
26 ethers generally having the reputation of causing various types  
27 of dermatitis. It is also known that the ethers are unpredictable  
28 in their bleaching effect and sometimes cause a progression of  
29 depigmentation after application has been stopped. Hydro-  
30 quinone is the agent of choice when a hydroquinone bleaching

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1 agent is desired for these reasons.

2 A 2% hydroquinone composition is commercially available  
3 under the trademark Eldoquin and Eldopaque by Paul Elder &  
4 Company. Hydroquinone is reported to be the sole active in-  
5 gredient.

6 In our hands, it has been found that a preparation con-  
7 taining only 2% hydroquinone is unpredictable and not always  
8 effective. Similar results have been reported in the literature  
9 (Clinical Medicine, 72, No. 3, 87-88 [March 1966]) wherein 35%  
10 of those subjects treated showed excellent results, 5% good,  
11 35% fair and 25% poor.

12 Subsequent investigations to improve these results were  
13 undertaken and it has been unexpectedly found that a composition  
14 containing hydroquinone, or a derivative thereof, in combination  
15 with a skin irritant-exfoliating agent and an anti-inflammatory  
16 corticosteroid produced good to excellent results in almost all  
17 of the subjects so treated. One must consider these results to  
18 be a type of synergism inasmuch as these superior results can  
19 not be achieved by any of the individual components alone.

20 The compositions of the present invention are applied  
21 according to the following general regimen. In the case of  
22 the formulation of example 1, the composition was applied two  
23 to three times daily to the areas to be bleached. The composi-  
24 tion is preferably applied three times a day for two days, then  
25 two times a day till irritation (mild inflammation) can be seen.  
26 Depending upon the degree of irritation, the composition is applied  
27 once or twice a day till depigmentation occurs. Depigmenta-  
28 tion usually begins to occur five to twenty-one days after the  
29 initial application. Depigmentation is usually complete within  
30 six to ten weeks.



In patients with recurrent hyperpigmentation (negroes, other dark-skinned races), pigmentation can be maintained by several applications per week.

The results produced by the application of the above composition are exceptionally good. In almost 100% of the subjects so treated, good to excellent depigmentation was obtained. The results were particularly dramatic in normal negro skin, wherein the skin was bleached white in the majority of subjects so treated.

Generally, similar results can be obtained with any of the formulations of the present inventions, although the frequency of application, the time required for depigmentation and the degree of depigmentation will vary with the components strength, and pharmaceutical vehicle used.

#### Examples of the Embodiments

##### Example 1

Hydroquinone	2%
Retinoic Acid	0.05%
Fluorometholone	0.025%
Fragrance q.s.	
Propylene glycol	
Ethanol (95%) H <sub>2</sub> O q.s. ad 100 ml.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone and dissolve in about 80 ml. of the 50:50 mixture of propylene glycol and ethanol. Add the fragrance and q.s. ad to 100 ml. Mix well and apply to area to be bleached.

##### Example 2

Substitution in the formula of example 1 for the fluoro-



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1 metholone used therein of 0.025% of dexamethasone produces an  
2 equivalent formulation.

3 Example 3

4  
5 Hydroquinone 2%  
6 Retinoic acid 0.05%  
7 Fluorometholone 0.025%  
8 Vanishing Cream base q.s. to 100 gm.

9  
10 Finally pulverize the hydroquinone, retinoic acid and fluoro-  
11 metholone. Add a small quantity of the vanishing cream base and  
12 mix well to obtain a gritless paste. Add additional vanishing  
13 cream base to make 100 gm. of product. Mix well and apply.

14  
15 Example 4

16 Hydroquinone 2%  
17 Retinoic acid 0.05%  
18 Fluorometholone 0.025%  
19 Emollient lotion q.s. to 100 ml.

20  
21 Finally pulverize the hydroquinone, retinoic acid and fluoro-  
22 metholone. Add a small quantity of the emollient lotion to the  
23 powder to make a gritless paste. Add sufficient lotion to make  
24 100 ml. Mix well and apply.

25  
26 Example 5

27 Hydroquinone 2%  
28 Retinoic acid 0.05%  
29 Hydrocortisone 2.5%  
30 Vanishing cream base q.s. to 100 gm.

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Prepare as in example 3.

Example 6

Hydroquinone	2%
n-Octylamine	0.5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Finally pulverize the hydroquinone and fluorometholone. Add the n-octylamine and a small quantity of vanishing cream to make a gritless paste. Add sufficient vanishing cream to make 100 gm. Mix well and apply.

Example 7

Hydroquinone	2%
Sodium lauryl sulfate	5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in example 3.

Example 8

Hydroquinone	2%
Linoleic acid	50%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95 %) q.s. ad 100 ml.	

Prepare as in example 1.

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Example 9

2	Hydroquinone	2%
3	Linolenic acid	55%
4	Fluorometholone	0.025%
5	Propylene glycol	
6	Ethanol (95%) BA q.s. ad 100 ml.	

8 Prepare as in example 1.

Example 10

11	Hydroquinone	2%
12	Arachidonic Acid	10%
13	Fluorometholone	0.025%
14	Propylene glycol	
15	Ethanol (95%) BA q.s. ad 100 ml.	

17 Prepare as in example 1.

Example 11

20	Hydroquinone	2%
21	Polyoxyethylene lauryl ether	10%
22	Fluorometholone	0.025%
23	Propylene glycol	
24	Ethanol (95%) BA q.s. ad 100 ml.	

26 Prepare as in example 1.

Example 12

28	Hydroquinone monobenzyl ether	5%
29	Retipic acid	0.05%



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1 Fluorometholone

0.025%

2 Vanishing cream base q.s. ad 100 gm.

3  
4 Prepare as in example 3.

5 Example 13

6  
7 Hydroquinone

5%

8 Retinoic acid

0.05%

9 Fluorometholone

0.05%

10 Vanishing cream base q.s. ad 100 gm.

11  
12 Prepare as in example 3.

13  
14 The above examples are illustrative of some of the variations  
15 in formulation that can be made within the scope of the present  
16 invention.

17 To prepare a more elegant or stable product, it may be de-  
18 sirable to incorporate fragrances, pigments, preservatives and/or  
19 a stabilizer including anti-oxidants, all of which are within the  
20 ability of those knowledgeable in the art.



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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A synergistic skin-bleaching composition for external application which comprises a mixture of about 1% to about 10% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monethyl ether and hydroquinone monobenzyl ether; about 0.025% to about 10% of retinoic acid as a skin irritant-exfoliating agent, and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid, formulated in a pharmaceutically-cosmetically acceptable vehicle.
2. A composition of claim 1 comprising about 1% to about 5% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monomethyl ether and hydroquinone monobenzyl ether, about 0.025% to about 10% of retinoic acid and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid selected from the group comprising hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.
3. A composition of claim 1 comprising about 1% to about 5% of hydroquinone, about 0.020% to about 10% of retinoic acid as an skin-irritant-exfoliating agent, and about 0.01% to about 3% of an anti-inflammatory corticosteroid selected from the group comprising dexamethasone, betamethasone, flucinoline, flucinolone acetonide, triamcinolone, hydrocortisone, triamcinolone acetonide, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

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4. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluorometholone formulated in a pharmaceutically-cosmetically acceptable vehicle.

5. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone formulated in a pharmaceutically-cosmetically acceptable vehicle.

6. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and about 2.5% hydrocortisone or hydrocortisone acetate formulated in a pharmaceutically-cosmetically acceptable vehicle.

7. A composition, as in claim 1 or 2, comprising hydroquinone, retinoic acid, and an anti-inflammatory corticosteroid.

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